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A Structured Framework to Establish and Evaluate Multidimensional Outcome Measures in Drug Development: A Conceptual Proposal

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ABSTRACT:
This paper proposes a structured framework to establish multidimensional outcome measures in drug development. In addition to clinical results, the outcome measure also take into consideration of patient health related quality of life (HRQOL) at different functional levels and acceptance from stakeholders such as clinicians, caregivers, patients, manufacturers, and payers. The outcome measures are evidence-based with clearly identified critical quality attributes (CQAs). The goal attainment of multidimensional outcome measures can be visually assessed using graphic illustrations, such as Radar chart. The master outcome measures (MOM) of a drug development program are defined by clinical results, patient HRQOL, and acceptance, which are further defined by sets of sub-level outcome measures. The outcome measures are validated using the following nine criteria: model development, appropriateness, reliability, validity, responsiveness, precision, interpretability, acceptability, and feasibility. Risk assessment and multivariable methods (design space) are used to establish the design space between outcome CQAs and critical/key factors using both forward (rationale-oriented) and backward (results-oriented) approaches. Outcome measures should be actively managed and updated throughout the drug product lifecycle.

Keywords: quality by testing (QbT), quality by design (QbD), outcome-driven approach, multidimensional outcome measures, Radar chart, health related quality of life (HRQOL), critical quality attribute (CQA), outcome validation, design space, multivariable methods, risk assessment, drug development, product lifecycle

INTRODUCTION

The traditional approach in drug development used to focus heavily on testing of drug product (Figure 1), which is sometimes referred to as the quality by testing (QbT) approach. The high variation and failure rate due to lack of control in the manufacturing process made people aware that "quality cannot be tested into products, it has to be built in by design" [1]. However, the drug industry lags behind other industries such as semiconductor industry in employing the quality by design (QbD) concept. The past decade saw the pharmaceutical industry started to embrace QbD methodologies in drug development process [2,3], which greatly enhanced the control in drug production process and dramatically reduced the different types of risks in the process. However, the current QbD approach focuses mainly on the CQAs of a drug product and the critical parameters of drug manufacturing process (Figure 1), without a systematic approach on defining outcome measures of drug development. Without a well-defined outcome, it is difficult to assess the value and quality potential of a drug program [4]. For example, many companies are still struggling on how to establish the CQAs of a drug product [5]. In the past, the best possible clinical results on medical conditions are automatically the target the development is shooting at. But do clinical results tell the whole story? As early as 2001, the PRO Harmonization Group task force report urged to incorporate the patient's perspective into drug development and communication, in addition to clinical results [6]. Until today, though the need for extensive outcome research beyond clinical results was well recognized [7], there is no consensus on how to establish the outcome measures in drug development.

This paper tried to explore the multidimensional outcome measures for drug development, with the objective to propose a structured framework to establish outcome measures in order to have balanced assessment in drug development. In addition to clinical results, we need to add other dimensions, such as patient HRQOL at different functional levels, and acceptance from different stakeholders such as clinicians, patients, caregivers, manufacturers, and payers.

OUTCOME-DRIVEN APPROACH IN DRUG DEVELOPMENT

In contrast to the traditional QbT and current QbD approaches, the outcome-driven approach targets the best possible results in not only clinical results, but also patient HRQOL and acceptance from different stakeholders, as illustrated in Figures 1 and 2. The clinical results will consider the efficacy, pharmacokinetics/pharmacodynamics (PK/PD), safety, immunogenicity of a drug product [8]. The patient HRQOL will take into consideration of factors affecting patient quality of life at different levels, namely cell/tissue level, organ level, individual level, and social (and environment) level. This covers a variety of patient feedback, such as emotional/mental health, social function, and general well being, on their experience and satisfaction when using a drug product in their daily life at different time frames. The acceptance will consider acceptance and preference from different stakeholders, namely patients,

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caregivers, clinicians, manufacturers, and payers. Thus, the outcome-driven approach takes a systematic look at overall outcomes in a drug development program from different perspectives and stakeholders.

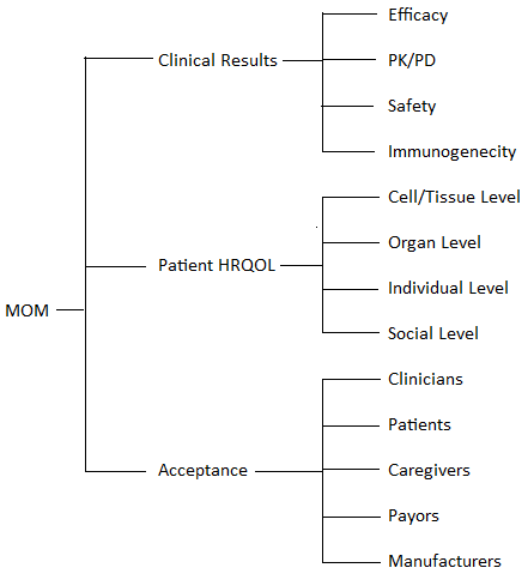

Figure 1. The Multidimensional Outcome Measures in Drug Development

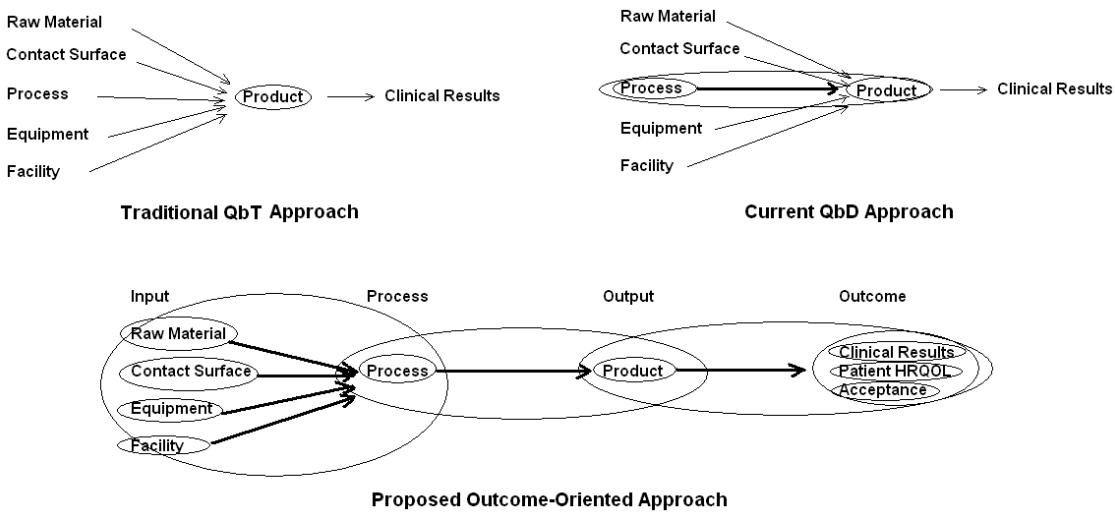

Figure 2. Different Approached in Drug Development. Quantitative multi-variable characterization is schematically illustrated by oval circles.

GRAPHIC ILLUSTRATION OF MULTIDIMENSIONAL OUTCOME MEASURES

Multidimensional outcome measures can be visualized by Radar chart, which is schematically illustrated in Figure 3. Each axis represents one dimension of an outcome. The length of an axis represents the total score, which is lined up with other total scores to form the total area of a set of outcome measures. The length of an axis may vary, depending on the pre-determined criticality of an outcome, though Figure 2 shows all the

axes are equivalent. The actual score of each outcome is also lined up to form the actual area of this set of outcome measures. The goal attainment can be assessed graphically by comparing the actual area (colored) to the total area, which will help to identify strength and weakness.

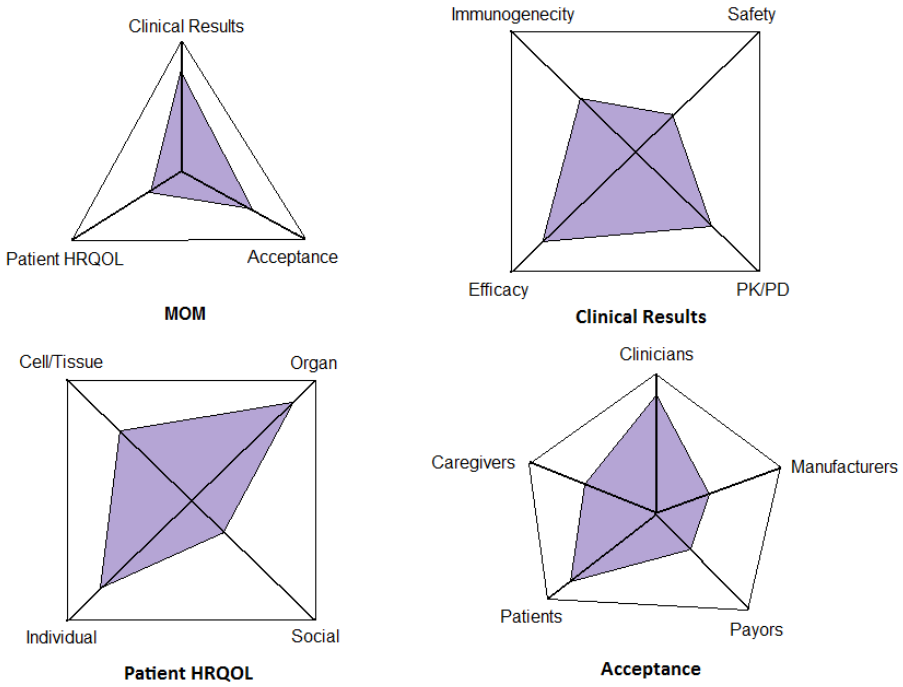

Figure 2. Schematic Illustration using Radar Chart to Evaluate Goal Attainment in Drug Development

MULTIDIMENSION OUTCOME MEASURES AT DIFFERENT LEVELS

The master outcome measures (MOM) define the overall goal of a drug development program, which is tentatively defined by three factors: clinical results, patient HRQOL, and acceptance. Each of these factors is the 2nd level of outcome measures, which is defined by a set of 3rd level of outcome measures, and so on (Figure 1). Alternatively, the fish bone diagram can be used to illustrate the relationship between the different levels of multidimensional outcome measures.

DEFINING OUTCOME MEASURES AND THEIR DETERMINANTS

Outcome measures are evidence-based with clearly identified CQAs using a combination of forward (rationale design) and backward (result-oriented) approaches (Figure 4). The initial outcome measures are established by the forward approach using a combination of methodologies such as rationale design, prior knowledge, and risk assessment, which, as more data become available in drug development, will be re-evaluated and updated by the backward approach using a combination of methodologies such as design space (with clearly defined CQAs), trending and distribution analysis, qualification and validation studies, etc. The link between outcome measures and the determinants should be established and well characterized by a variety of quantitative multi-variable methods to ensure it is well understood and well controlled with minimal variation (Table 1).

Risk assessment should be conducted throughout the product lifecycle (Figure 4). The commonly used risk assessment tools, such as failure mode and effect analysis (FMEA) and hazard analysis and critical control point (HACCP), are not appropriate to assess risks in early development stages as these tools may take off risks too early due to low scores on occurrence and/or detection based on assumption or limited data [5]. Instead, there are several proposed tools for early CQA assessment. For example, the one proposed by Genetech is to assess the criticality of each quality attribute by impact and uncertainty on drug safety and efficacy, while the other one proposed by MedImmune assesses the criticality by severity and likelihood instead [8]. As more data become available, more comprehensive risk assessment programs with quantitative risk calculation and sufficient control strategy should be established to assess the real risks in every aspect of product production and delivery.

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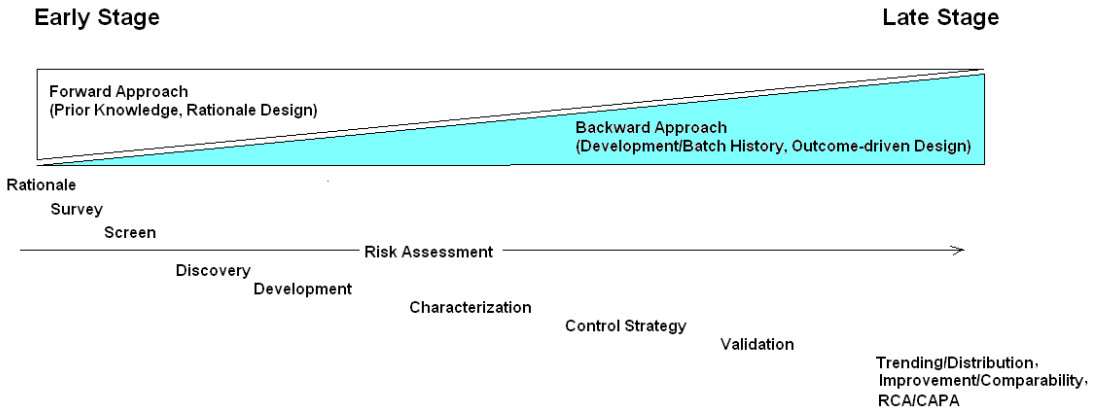

Figure 4. Approaches and Methodologies Employed in Early and Late Stage Drug Development

Table 1. Quantitative Multi-variable Characterization in Drug Development

Task	Description	Goal	Methods
Outcome Characterization	-Criticality -Variability -Controllability -Acceptability	The goal of characterization is to establish well-understood (CQAs and effects) and well-controlled (parameters and ranges) process to produce expected outcome with minimal variation.	-Comprehensive risk management program (systematic risk assessment, control strategy, comprehensive review, etc.) -Design space (DOE) -Robustness studies -Challenging studies -Trending and Distribution analysis -Process analytical technology (PAT)
Product Characterization	-Structure (primary structure, secondary and high order structure) -Pre-formulation -Stability -Function (activity, potency, etc.)		
Process Characterization	-Microbiology (Cell Bank, Seed Culture) -Fermentation (Culture, Harvest) -Purification (Chromatography, Precipitation, Filtration) -Formulation		
Raw Material Characterization	-Component (Complex, Simple, Source) -Impurities -Effect (Physical, Biological)		
Contact Surface Characterization	-Component (Complex, Simple, Source) -Impurities -Leachables -Extractables -Effect (Physical, Biological)		
Equipment Characterization	-Design -Installation -Operation -Performance -Calibration		
Facility Characterization	-Design (Work Segregation, Air Flow and Quality, Consumables, Wastes, HVAC, etc.) -Operation (Clean, Maintenance, Upgrade, Monitor) -Performance (Environment, Breach, Safety, Security)		

VALIDATING OUTCOME MEASURES

Outcome measures should be carefully developed so that they serve the intended purpose of setting appropriate goals in drug development. A systematic process should be followed to take into consideration of different factors in across the different perspectives from drug development to intended use, which involve item generation, testing, item reduction, and scale development. The outcome measures need to be validated to ensure it is appropriate and serves their intended purposes. As proposed by [9–11], the following nine criteria can be used in outcome measure validation: scale development, appropriateness, reliability, validity, responsiveness, precision, interpretability, acceptability, and feasibility (Table 2). While general concept can be followed in developing outcome measures, they cannot be used indiscriminately without considering the specific situations in individual cases. Also, there is no scale that ideally satisfies all the criteria, hence, drug developers need to consider the relative advantage and limitations of various outcome measures and develop the measures best suit their needs.

Table 2. Evaluation Criteria for Outcome Measures

Criteria	Definition	Establishing Methods
Scale	Effect size in an outcome measure	Systematic process (follow the steps of item generation, initial item reduction, testing, final item reduction, establishing scale measurement properties)
Appropriateness	Comparing an outcome measure to its intended purpose	Rationale, review
Reliability (Internal consistency and reproducibility)	Compares random error to the true effect	Internal consistency and reproducibility Interclass correlation coefficient (ICC), Cronbach's alpha 0.7 – 0.9, Pearson r correlation coefficient
Validity (criterion, face/content, construct)	Ability of an instrument to measure intended outcome	Comparison to "gold standard", concurrent and predictive, outcome, construct
Responsiveness	Ability to detect change over time when changes happen	Change score, effect size, standardized response mean (SRM), modified SRM, relative efficiency, sensitivity and specificity, ceiling and floor effects
Precision	Consistency among individual measurements	binary, likert, VAS
Interpretability	Ability to interpret the meaning of the scores	Rationale, design, feedback
Acceptability	Ease to provide feedback	Rationale, design, feedback
Feasibility	Ease to administer	Rationale, design, feedback

Note. Prepared based on references [9-11]. The table title was revised on February 20, 2012 from the originally published manuscript.

CONCLUSION

This paper proposes an outcome-driven approach in drug development and a structured framework to establish multidimensional outcome measures at different levels. In addition to clinical results, the outcome measure also take into consideration of patient HRQOL at different functional levels and acceptance from stakeholders such as clinicians, caregivers, patients, manufacturers, and payers. The goal attainment of the outcome measures can be graphically illustrated by Radar chart. The outcome measures are defined using a combination of forward and backward approach at different stages in drug development. The outcome measures need to be validated to ensure they are appropriate and serve the intended purposes. This is merely a conceptual proposal, drug developers need to consider the relative advantage and limitations of various outcome measures and develop the measures best suit their needs.

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